CLAIMS

1. A conjugate comprising:

(a) a polypeptide having the amino acid sequence :

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,

m equals 1 or 2;

n is an integer from 1 to 50;

S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;

Z is any amino acid residue excepting serine residue or threonine residue; and

X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue; and

(b) at least one hydrophobic moiety being attached to said polypeptide,

the conjugate being capable of inhibiting an activity of glycogen synthase kinase-3 (GSK-3), wherein the hydrophobic moiety provides the conjugate with better (i) membrane permeability and/or (b) interaction with the hydrophobic patch of the GSK-3.

2. The conjugate of claim 1, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

3. The conjugate of claim 1, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

4. The conjugate of claim 1, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

5. The conjugate of claim 4, wherein said hydrophobic peptide sequence comprises at least five amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine

residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

6. The conjugate of claim 1, wherein said at least one hydrophobic moiety comprises a fatty acid.

7. The conjugate of claim 6, wherein said fatty acid is attached to at least one amino acid residue.

8. The conjugate of claim 6, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

9. The conjugate of claim 8, wherein said fatty acid is myristic acid.

10. The conjugate of claim 1, wherein Y_3 is any amino acid residue except a glutamic acid residue.

11. The conjugate of claim 1, wherein Z is an alanine residue.

12. The conjugate of claim 1, wherein n is an integer from 1 to 15.

13. The conjugate of claim 12, wherein n is an integer from 1 to 10.

14. The conjugate of claim 1, having the amino acid sequence set forth in SEQ ID NO:16.

15. A pharmaceutical composition comprising, as an active ingredient, the conjugate of claim 1, and a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, packaged in a packaging material and identified in print, on or in said packaging material, for use in the treatment of a biological condition associated with GSK-3 activity.

17. The pharmaceutical composition of claim 16, wherein said biological condition is selected from the group consisting of obesity, non-insulin dependent diabetes mellitus, an insulin-dependent condition, an affective disorder, a neurodegenerative disease or disorder and a psychotic disease or disorder.

18. The pharmaceutical composition of claim 17, wherein said affective disorder is selected from the group consisting of a unipolar disorder and a bipolar disorder.

19. The pharmaceutical composition of claim 18, wherein said unipolar disorder is depression.

20. The pharmaceutical composition of claim 18, wherein said bipolar disorder is manic depression.

21. The pharmaceutical composition of claim 17, wherein said neurodegenerative disorder results from an event selected from the group consisting of cerebral ischemia, stroke, traumatic brain injury and bacterial infection.

22. The pharmaceutical composition of claim 17, wherein said neurodegenerative disorder is a chronic neurodegenerative disorder.

23. The pharmaceutical composition of claim 22, wherein said chronic neurodegenerative disorder results from a disease selected from the group consisting of Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS associated dementia, amyotrophic lateral sclerosis (AML) and multiple sclerosis.

24. The pharmaceutical composition of claim 15, further comprising at least one additional active ingredient that is capable of altering an activity of GSK-3.

25. The pharmaceutical composition of claim 24, wherein said additional active ingredient is insulin.

26. The pharmaceutical composition of claim 24, wherein said additional active ingredient is capable of inhibiting an activity of GSK-3.

27. The pharmaceutical composition of claim 26, wherein said additional active ingredient is selected from the group consisting of a GSK-3 inhibitor, lithium, valproic acid and a lithium ion.

28. The pharmaceutical composition of claim 24, wherein said additional active ingredient is capable of downregulating an expression of GSK-3.

29. The pharmaceutical composition of claim 28, wherein said additional active ingredient is a polynucleotide.

30. The pharmaceutical composition of claim 29, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

31. The pharmaceutical composition of claim 30, wherein said small interfering polynucleotide molecule is selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

32. The pharmaceutical composition of claim 15, formulated in a delivery form selected from the group consisting of aerosol, aqueous solution, bolus, capsule, colloid, delayed release, depot, dissolvable powder, drops, emulsion, erodible implant, gel, gel capsule, granules, injectable solution, ingestible solution, inhalable solution, lotion, oil solution, pill, suppository, salve, suspension, sustained release, syrup, tablet, tincture, topical cream, transdermal delivery form.

33. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

34. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

35. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

36. The pharmaceutical composition of claim 35, wherein said hydrophobic peptide sequence comprises at least five amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

37. The pharmaceutical composition of claim 15, wherein said at least one hydrophobic moiety comprises a fatty acid.

38. The pharmaceutical composition of claim 37, wherein said fatty acid is attached to at least one amino acid residue.

39. The pharmaceutical composition of claim 37, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

40. The pharmaceutical composition of claim 39, wherein said fatty acid is myristic acid.

41. The pharmaceutical composition of claim 15, wherein Y_3 is any amino acid residue except a glutamic acid residue.

42. The pharmaceutical composition of claim 15, wherein Z is an alanine residue.

43. The pharmaceutical composition of claim 15, wherein n is an integer from 1 to 15.

44. The pharmaceutical composition of claim 43, wherein n is an integer from 1 to 10.

45. The pharmaceutical composition of claim 15, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

46. A method of inhibiting an activity of GSK-3, the method comprising contacting cells expressing GSK-3 with an effective amount of the conjugate of claim 1.

47. The method of claim 46, wherein said activity is a phosphorylation activity and/or an autophosphorylation activity.

48. The method of claim 46, wherein said contacting is effected *in vitro*.

49. The method of claim 46, wherein said contacting is effected *in vivo*.

50. The method of claim 46, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

51. The method of claim 46, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

52. The method of claim 46, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

53. The method of claim 52, wherein said hydrophobic peptide sequence comprises at least five amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

54. The method of claim 46, wherein said at least one hydrophobic moiety comprises a fatty acid.

55. The method of claim 54, wherein said fatty acid is attached to at least one amino acid residue.

56. The method of claim 54, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

57. The method of claim 56, wherein said fatty acid is myristic acid.

58. The method of claim 46, wherein Y_3 is any amino acid residue except a glutamic acid residue.

59. The method of claim 46, wherein Z is an alanine residue.

60. The method of claim 46, wherein n is an integer from 1 to 15.

61. The method of claim 60, wherein n is an integer from 1 to 10.

62. The method of claim 46, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

63. The method of claim 46, further comprising contacting said cells with at least one an additional active ingredient, said additional active ingredient being capable of altering an activity of GSK-3.

64. The method of claim 63, wherein said additional active ingredient is insulin.

65. The method of claim 63, wherein said additional active ingredient is capable of inhibiting an activity of GSK-3.

66. The method of claim 65, wherein said additional active ingredient is selected from the group consisting of a GSK-3 inhibitor, lithium, valproic acid and a lithium ion.

67. The method of claim 63, wherein said additional active ingredient is capable of downregulating an expression of GSK-3.

68. The method of claim 67, wherein said additional active ingredient is a polynucleotide.

69. The method of claim 68, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

70. The method of claim 69, wherein said small interfering polynucleotide molecule is selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

71. A method of potentiating insulin signaling, the method comprising contacting insulin responsive cells with an effective amount of the conjugate of claim 1.

72. The method of claim 71, further comprising contacting said cells with insulin.

73. The method of claim 71, wherein said contacting is effected *in vitro*.

74. The method of claim 71, wherein said contacting is effected *in vivo*.

75. The method of claim 71, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

76. The method of claim 71, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

77. The method of claim 71, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

78. The method of claim 77, wherein said hydrophobic peptide sequence comprises at least five amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine

residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

79. The method of claim 71, wherein said at least one hydrophobic moiety comprises a fatty acid.

80. The method of claim 79, wherein said fatty acid is attached to at least one amino acid residue.

81. The method of claim 79, wherein said at least one fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

82. The method of claim 81, wherein said fatty acid is myristic acid.

83. The method of claim 71, wherein Y_3 is any amino acid residue except a glutamic acid residue.

84. The method of claim 71, wherein Z is an alanine residue.

85. The method of claim 71, wherein n is an integer from 1 to 15.

86. The method of claim 85, wherein n is an integer from 1 to 10.

87. The method of claim 71, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

88. Use of the conjugate of claim 1 for treating a biological condition associated with GSK-3 activity.

89. The use of claim 88, wherein said biological condition is selected from the group consisting of obesity, non-insulin dependent diabetes mellitus, an insulin-dependent condition, an affective disorder, a neurodegenerative disease or disorder and a psychotic disease or disorder.

90. The use of claim 89, wherein said affective disorder is selected from the group consisting of a unipolar disorder and a bipolar disorder.

91. The use of claim 90, wherein said unipolar disorder is depression.

92. The use of claim 90, wherein said bipolar disorder is manic depression.

93. The use of claim 89, wherein said neurodegenerative disorder results from an event selected from the group consisting of cerebral ischemia, stroke, traumatic brain injury and bacterial infection.

94. The use of claim 89, wherein said neurodegenerative disorder is a chronic neurodegenerative disorder.

95. The use of claim 94, wherein said chronic neurodegenerative disorder results from a disease selected from the group consisting of Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS associated dementia, amyotrophic lateral sclerosis (AML) and multiple sclerosis.

96. The use of claim 89, wherein said psychotic disorder is schizophrenia.

97. The use of claim 88, further comprising use of at least one additional active ingredient, said at least one additional active ingredient being capable of altering an activity of GSK-3.

98. The use of claim 97, wherein said additional active ingredient is insulin.

99. The use of claim 97, wherein said additional active ingredient is capable of inhibiting an activity of GSK-3.

100. The use of claim 99, wherein said additional active ingredient is selected from the group consisting of a GSK-3 inhibitor, lithium, valproic acid and a lithium ion.

101. The use of claim 97, wherein said additional active ingredient is capable of downregulating an expression of GSK-3.

102. The use of claim 101, wherein said additional active ingredient is a polynucleotide.

103. The use of claim 102, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular GSK-3 mRNA degradation.

104. The use of claim 103, wherein said small interfering polynucleotide molecule is selected from the group consisting of an RNAi molecule, an anti-sense molecule, a rybozyme molecule and a DNAzyme molecule.

105. The use of claim 88, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

106. The use of claim 88, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

107. The use of claim 88, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

108. The use of claim 107, wherein said hydrophobic peptide sequence comprises at least five amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

109. The use of claim 88, wherein said at least one hydrophobic moiety comprises a fatty acid.

110. The use of claim 109, wherein said fatty acid is attached to at least one amino acid residue.

111. The use of claim 109, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

112. The use of claim 111, wherein said fatty acid is myristic acid.

113. The use of claim 88, wherein Y_3 is any amino acid residue except a glutamic acid residue.

114. The use of claim 88, wherein Z is an alanine residue.

115. The use of claim 88, wherein n is an integer from 1 to 15.

116. The use of claim 115, wherein n is an integer from 1 to 10.

117. The use of claim 88, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

118. Use of at least one compound that is capable of specifically inhibiting an activity of GSK-3 for the treatment of an affective disorder.

119. The use of claim 118, wherein said affective disorder is selected from the group consisting of a unipolar disorder and bipolar disorder.

120. The use of claim 119, wherein said unipolar disorder is depression.

121. The use of claim 119, wherein said bipolar disorder is manic depression.

122. The use of claim 118, wherein said compound is a polypeptide having the amino acid sequence:

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,
m equals 1 or 2;
n is an integer from 1 to 50;
S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;
Z is any amino acid residue excepting serine residue or threonine residue; and
X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue.

123. The use of claim 122, wherein Y_3 is any amino acid residue except a glutamic acid residue.

124. The use of claim 122, wherein Z is an alanine residue.

125. The use of claim 122, wherein n is an integer from 1 to 15.

126. The use of claim 125, wherein n is an integer from 1 to 10.

127. The use of claim 122, wherein said polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:12.

128. The use of claim 122, wherein said polypeptide further comprises at least one hydrophobic moiety being attached thereto.

129. The use of claim 128, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

130. The use of claim 128, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

131. The use of claim 128, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

132. The use of claim 131, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

133. The use of claim 128, wherein said at least one hydrophobic moiety comprises a fatty acid.

134. The use of claim 133, wherein said fatty acid is attached to at least one amino acid residue.

135. The use of claim 133, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

136. The use of claim 135, wherein said fatty acid is myristic acid.

137. The use of claim 128, wherein Y_3 is any amino acid residue except a glutamic acid residue.

138. The use of claim 128, wherein Z is an alanine residue.

139. The use of claim 128, wherein n is an integer from 1 to 15.

140. The use of claim 139, wherein n is an integer from 1 to 10.

141. The use of claim 128, wherein said compound has the amino acid sequence set forth in SEQ ID NO:16.

142. A use of at least one compound that is capable of specifically inhibiting an activity of GSK-3 for up-regulating a β-catenin level in a hippocampus of a subject.

143. The use of claim 142, wherein said compound is a polypeptide having the amino acid sequence:

$$[Yn\cdots Y_1]ZX_1X_2X_3S(p)[W_1\cdots Wm]$$

wherein,

m equals 1 or 2;

n is an integer from 1 to 50;

S(p) is a phosphorylated serine residue or a phosphorylated threonine residue;

Z is any amino acid residue excepting serine residue or threonine residue; and

X_1, X_2, X_3, Y_1-Yn and W_1-Wm are each independently any amino acid residue.

144. The use of claim 143, wherein Y_3 is any amino acid residue except a glutamic acid residue.

145. The use of claim 143, wherein Z is an alanine residue.

146. The use of claim 143, wherein n is an integer from 1 to 15.

147. The use of claim 146, wherein n is an integer from 1 to 10.

148. The use of claim 143, wherein said polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequences set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:12.

149. The use of claim 143, wherein said polypeptide further comprises at least one hydrophobic moiety being attached thereto.

150. The use of claim 149, wherein said at least one hydrophobic moiety is attached to an N-terminus and/or a C-terminus of said polypeptide.

151. The use of claim 149, wherein said at least one hydrophobic moiety is attached to an N-terminus of said polypeptide.

152. The use of claim 149, wherein said at least one hydrophobic moiety comprises a hydrophobic peptide sequence.

153. The use of claim 152, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

154. The use of claim 149, wherein said at least one hydrophobic moiety comprises a fatty acid.

155. The use of claim 154, wherein said fatty acid is attached to at least one amino acid residue.

156. The use of claim 154, wherein said fatty acid is selected from the group consisting of myristic acid, lauric acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

157. The use of claim 156, wherein said fatty acid is myristic acid.

158. The use of claim 149, wherein Y_3 is any amino acid residue except a glutamic acid residue.

159. The use of claim 149, wherein Z is an alanine residue.

160. The use of claim 149, wherein n is an integer from 1 to 15.

161. The use of claim 160, wherein n is an integer from 1 to 10.

162. The use of claim 149, wherein said compound has the amino acid sequence set forth in SEQ ID NO:16.

163. A process of producing the conjugate of claim 1, the process comprising:
providing said polypeptide;
providing said at least one hydrophobic moiety; and
conjugating said at least one hydrophobic moiety and said polypeptide.

164. The process of claim 163, wherein said providing of said polypeptide is by chemically synthesizing said polypeptide.

165. The process of claim 163, wherein said providing of said polypeptide is by recombinantly producing said polypeptide.

166. The process of claim 163, wherein said conjugate has the amino acid sequence set forth in SEQ ID NO:16.

167. The conjugate of claim 4, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

168. The conjugate of claim 4, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

169. The pharmaceutical composition of claim 35, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

170. The pharmaceutical composition of claim 35, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

171. The method of claim 52, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group

consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

172. The method of claim 52, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

173. The method of claim 77, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

174. The method of claim 77, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

175. The use of claim 107, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a cysteine residue, a glycine residue, an isoleucine residue, a leucine residue, a valine residue, a phenylalanine residue, a tyrosine residue, a methionine residue, a proline residue and a tryptophan residue.

176. The use of claim 107, wherein said hydrophobic peptide sequence comprises at least five consecutive amino acid residues selected from the group consisting of an alanine residue, a glycine residue, a leucine residue, a valine residue, and a proline residue.

177. Use of the conjugate of claim 1 for the preparation of a medicament for the treatment of a biological condition associated with GSK-3 activity.

178. Use of at least one compound that is capable of specifically inhibiting an activity of GSK-3 for the preparation of a medicament for the treatment of an affective disorder.